UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/125,751	10/30/1998	OYSTEIN FODSTAD	4885.55USWO	8143

23552 7590 10/01/2002

MERCHANT & GOULD PC
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/125,751	Fostad
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *one* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 3, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3, 6-8, 14-17, 19-22, and 24* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3, 6-8, 14-17, 19-22, and 24* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Amendment filed June 24, 2002 (Paper No. 24) in response to the Office Action of March 26, 2002 (Paper No. 23) is acknowledged and has been entered. Previously pending claims 1, 3, 15, 20 and 24 have been amended. It is noted that claim 24 was previously canceled in Paper No. 22 (please see Paper No.23, page 1). Claims 1, 3, 6-8, 13-16, 18-23, 25-26 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following objection is maintained:

Objection to amendment of the specification is maintained.

Applicant argues that claim 1 of the PCT parent of this National Stage application supports the newly added material. The argument has been considered but has not been found persuasive because claim 1 of the PCT application is not drawn to any immunotoxin that is "directed to epitopes on a combination of these". Applicant is required to cancel the new matter in response to this Office action.

4. The following rejections are maintained:

Claim Rejections - 35 USC § 112

5. Claims 1, 3, 6-8, 20 and 25-26 remain rejected under 35 USC 112, second paragraph for the reasons previously set forth in Paper No. 23, Section 10, page 8.

Applicant argues that the term "active toxin fragment" would be clear and definite to one skilled in the art upon reading the specification. The argument has been considered but has not been found persuasive because "active toxin fragment" is not defined either by the specification or the claims as currently constituted..

New Grounds of Rejection

Claim Rejections - 35 USC § 112

6. Claims 1, 6-8, 13-14, 20-23, 25-26 are rejected under 35 USC 112, first paragraph essentially for the reasons previously set forth in Paper No. 23, Section 4, pages 3-6 because the specification, while being enabling for a method of killing breast cancer cells or other carcinoma cells *in vivo* and *ex vivo* wherein the method comprises incubation with MOC31-PE and BM2-PE, does not reasonably provide enablement for a method of killing breast cancer cells or other carcinoma cells *in vivo* and *ex vivo* wherein the method comprises incubation with immunotoxins directed against an EGP2 antigen and a MUC1 antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reasons previously set forth drawn to MOC31-PE and BM7-PE since the specification clearly states that BM2-PE binds to a sugar containing epitope on the same antigen as BM7-PE and shows approximately the same effectivity as BM7-PE concomitant with very low toxicity for normal cells.

Applicant's arguments drawn to the rejection of 1, 6-8, 13-14, 20-23, 25-26 in Paper No. 23 are relevant to the instant rejection.

Applicant argues that (a) one skilled in the art would recognize that immunotoxins specific for tumor cells would be more toxic to tumor cells than normal cells, (b) the ability of MOC31-PE and BM-7-PE to preferentially kill tumor cells is likely to do with the higher level of expression of the EPG2 and MUC1 antibodies and more rapid internalization of the antibody, not because MOC31 and MB7 are selective for antigen expressed on tumor cells. These antibodies recognize

antigen expressed on both tumor cells and normal cells, however they are toxic to tumor cells at concentrations that are not toxic to normal cells, (c) the combination of MOC31 and BM2 produced surprisingly greater than additive effects in killing breast cancer cells as shown on Table 1 of the specification. The combination surprisingly works well for immunotoxins that have differing activity when used alone, thus a combination of MUC1 and EPG2 antigens produces surprisingly high toxic activity toward tumor cells, (d) MOC31 recognizes the EPG2 antigen on both normal and tumor cells, (e) it is not appropriate for Examiner to reject the present claims because MOC31 is currently being sold for research purposes, simply because therapeutic use of MOC31 has not been approved, this determination is not appropriate for the USPTO.

The arguments have been considered but have not been found persuasive because (a') the claims are not limited to BM7-PE and MOC31-PE, (b') Apostolopoulos et al specifically teach that MUC-1 is highly expressed in breast cancer and due to altered glycosylation, peptides within the VNTR are exposed. These peptides are the target for anti-MUC1 antibodies which give a differential reaction on cancer compared with normal tissue. Further, the specification specifically teaches that BM7-PE binds to the protein part of a mucin antigen which mainly is found on breast cancer cells, suggesting that the epitope of BM7-PE is within the area exposed by altered glycosylation. Further, McClaughlin et al specifically teach that MOC31 specifically localizes to EGP-2 positive tumors but does not localize in normal tissues. Therefore, contrary to Applicant's arguments, it does not appear that the effectiveness and selectivity of the antibodies is due to

higher levels of expression or internalization, but rather to differences in epitopes exposed on the cancer cell as compared to normal cell antigens. Further, the claims as amended are drawn to BM2 which is known in the art to be specific and selective for a breast cancer tumor associated glycoprotein, (c') given the "surprising" nature of the results, it cannot be predicted that other combinations of antibodies to epitopes that are not limited to breast cancer cells would function as claimed, (d') Applicant is invited to present objective evidence supporting the hypothesized mechanism of action and demonstrating that MOC31 binds to normal cells, especially in view of the teaching of McClaughlin et al above, (e') although the USPTO does not determine the approval of the use of an immunotoxin for therapeutic purposes, it is a matter of public record that the MOC31 antibody is for research use only. The public record clearly demonstrates that the claimed invention does not meet the requirements of 35 USC 112, first paragraph for a method of treatment. The arguments presented are not persuasive to overcome the new grounds of rejection.

7. Claims 3, 15, 16, 18, 19 are rejected under 35 USC 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

The claim is drawn to monoclonal antibodies BM2 conjugated to a toxin.

It is unclear if cell lines which produce antibodies having the exact structural and chemical identity of BM2 are known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to a hybridoma cell line producing monoclonal antibody BM2, it would not be possible to practice the claimed invention. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. a similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species, BM2. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Applicant has not disclosed the deposit of hybridoma cell lines that would reproduce the antibody species BM2.

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications. Applicant's provision of these assurances would obviate this objection/rejection.

Affidavits and declarations, such as those under 37 C.F.R. § 1.131 and 37 C.F.R. § 1.132, filed during prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit, the applicant should make the remarks of record in the later application and include a copy of the original affidavit filed in the parent application

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of the deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Applicant's argument drawn to the rejection of the newly amended claims is relevant to the instant rejection. Applicant states that "As BM2 is a publicly available antibody that can be readily obtained.....withdrawal of the rejection is respectfully requested". The argument has been considered but has not been found persuasive because no evidence has been submitted demonstrating the public availablilty of the claimed antibody. Applicant is invited to submit objective evidence demonstrating that the BM2 antibody claimed is publicly available.

8. Claims 3, 15, 16, 18, 19 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 15 and the claims dependent upon claims 3 and 15 are indefinite in the recitation of antibody BM2 as the sole means of identifying the claimed antibodies. The use of laboratory designations only to identify a particular

antibody/cell line renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct hybridomas and antibodies. Amendment of the claims to include the depository accession number of the mAb or hybridoma is required, because deposit accession numbers are unique identifiers which unambiguously define a given hybridoma and/or monoclonal antibody.

Applicant's argument drawn to the rejection of the newly amended claims is relevant to the instant rejection. Applicant states that "As BM2 is a publicly available antibody that can be readily obtained.....withdrawal of the rejection is respectfully requested". The argument has been considered but has not been found persuasive because no evidence has been submitted demonstrating the public availablilty of the claimed antibody. Applicant is invited to submit objective evidence demonstrating that the BM2 antibody claimed is publicly available.

Claim Rejections - 35 USC § 103

9. Claims 1, 13, 14, 24 are rejected under 35 USC 103 for the reasons previously set forth in Paper No. 20, Section 9, pages 5-7.

Applicant's arguments drawn to the newly amended claims are relevant to the instant rejection.

Applicant argues that (a) unexpected synergy between MOC31 and BM2 has been demonstrated, (b) MOC31 and BM7 both bind tumor cells and normal cells. The argument has been considered but has not been found persuasive because (a') and (b') the claims are not limited to MOC31 and BM7 or BM2.

10. All other objections and rejections recited in Paper No. 23 are withdrawn.

11. No claims allowed.

12. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

a SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT a FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1640.

Susan Ungar
Primary Patent Examiner
August 26, 2002